PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants	:	Charles L. Magness and Shawn P. Iadonato
Application No.	:	09/707,576
Filed	:	November 6, 2000
For	:	SYSTEM AND METHOD FOR SELECTIVELY CLASSIFYING A POPULATION

Examiner	:	Anna Skibinsky
Art Unit	:	1631
Docket No.	:	55382-3
Date	:	August 16, 2006

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Affidavit of Shawn Iadonato, Ph.D. under 37 C.F.R. § 1.132

I, Shawn Iadonato, Ph.D. being duly sworn, say:

1. I am an internationally recognized scientist and at the time of filing the above-referenced patent application I was employed as Vice-President and Chief Scientific Officer, at Illumigen Biosciences, Inc., Seattle, WA. I received a Bachelors Degree in Biology from the University of Pennsylvania in Philadelphia and a Ph.D. degree from in Genetics from the University of Washington.

2. I am an author or co-author of numerous peer-reviewed research articles and have been invited to give numerous presentations on my research at national and international meetings. Prior to joining Illumigen, I managed sequence data collection

for the University of Washington Genome Center. My curriculum vitae is attached as Exhibit 1.

3. In my capacity as Founder, Vice-President, and Chief Scientific Officer, I manage the scientific and drug development programs of Illumigen. I have more than eight years experience developing and managing large-scale genetics and genomics projects, most notably involving my work on the Human Genome Project.

4. On information and belief, claims of the present application have been rejected under 35 U.S.C. § 112, first paragraph. According to the Office Action dated June 16, 2006, claims 1-10, 14-26, 28, 31-44 and 46-55 fail to comply with the enablement requirement because allegedly there is "undue experimentation required to go from the classification results achieved by implementing the invention to drug target identification without some prior knowledge of a relationship between a potential target and a biological condition as claimed." The experiments and results described in paragraphs 5-12 below support the enablement of the claimed invention by showing clearly that undue experimentation was not required to identify a drug target using the methods of the invention. In fact, following the methods of the present invention in a hepatitis C study, we found more than one drug target. The first of these was identified with an extremely short period of laboratory work (see 8. below) thus supporting the claim that the invention was sufficiently enabled and it did not require undue experimentation.

5. Illumigen's first drug is an anti-viral therapy for hepatitis C, and the drug is undergoing important pre-clinical studies; Phase I trials are scheduled for 2007. The drug was developed by following the methods as explicitly described in the present patent application.

6. In Step 1, recruiting of patients was performed from among populations at high risk for hepatitis C infection, specifically intravenous drug users and hemophiliacs. Over 3,500 subjects were screened, and a group of serially exposed and seronegative subjects was identified. These subjects correspond exactly to the ARU "at risk,

unaffected" population of the claims and the specification.

7. In Step 2, we sequenced a fraction of the genome of case (ARU) and control (ARA) subjects. These case and control subjects correspond exactly to the at risk and unaffected (exposed to hepatitis C and not currently infected with the virus) and at risk and affected (exposed to hepatitis C and currently infected with the virus) populations of the application and claims. Using the computer-based, genetic association methods like those disclosed in the application, genetic mutations associated with the "at risk and unaffected" ARU group were identified. These mutations affect a protein which corresponds to the "target" of the claims and the specification.

8. The mutations identified in step 2 of paragraph 7 above were discovered in a very short period of time with minimal resources, supporting the enablement of the methods of the invention. Illumigen's laboratory only began operation in January, 2003 and initiated DNA sequence analysis of the ARU and ARA groups in March, 2003. On October 23, 2003, a provisional application was submitted to the USPTO concerning our first drug target and detailing the primary functional mutation. The laboratory work supporting the computational genetic analysis was conducted using a single sequencing instrument and approximately one full-time-equivalent laboratory technician. Thus, while additional validating analyses were conducted after this date and drug optimization and testing has occurred over the succeeding three years, the limited amount of laboratory work that was conducted for primary identification of a drug target is highly supportive of enablement.

9. The mutation affects a gene involved in the interferon pathway; the gene encodes a protein known as OAS1. Using the information that mutated forms of OAS1 were expressed in the ARU group but not the ARA group, we developed an optimized form of the protein expressed by the mutated gene and tested it in an *in vitro* model of HCV infection; this protein corresponds to the therapeutic of the specification and the claims. As shown in Exhibit 2, the therapeutic protein, referred to as IB657, inhibits

EMCV infection of hepatoma (Huh7) cells.

10. On information and belief, the Office Action at page 10, lines 16-17, alleges that "the method of identifying a drug target based on genetic differences between two groups is not trivial and requires years to complete..." Although I agree that identifying a drug target is not "trivial," as it in fact is a major breakthrough, I strongly disagree that it takes years to complete. By following the methods described in this application, we identified a drug target (the mutated gene OAS1) initially in about seven months and a drug in about three years from start to preclinical drug candidate. A single cycle of data input, review and analysis according to the invention led directly to this drug discovery.

11. On information and belief, the Office Action at page 10, lines 14-15, alleges that "the identification of a drug target requires the sorting out of 1000's of targets present in most organisms." What applicants have disclosed and claimed is not the current method of target and drug discovery, but new methods. The drug currently undergoing preclinical testing, as described in paragraph 9 above, was developed at a fractional cost of the conventional approach. Furthermore, in addition to the cost benefit, the drug has entirely different toxicity parameters. The drug is based on studying ARU populations who already express a version of the drug and enjoy the beneficial effects of having it in their system. Therefore, the drug we developed is expected to have negligible toxicity compared to traditional drugs based on synthetic chemistry approaches. Thousands of targets were not "sorted out." The ARA and ARU comparison of the invention obviates that kind of historically laborious effort.

12. The drug that is the subject of paragraphs 9 and 10 above is one of many polypeptides disclosed and claimed in our subsequent co-pending patent application, Serial No. 10/972,135. The polypeptide of SEQ ID NO:48 has been found to be free of the art.

13. The 10/972,135 application was granted Special Status in a Decision on

Petition granted on December 7, 2005. The ground for the Petition was that applicant Illumigen is a Small Entity and the subject matter of the application is a major asset of the company. The Small Entity status of the company and the granting of the Petition to Make Special in the co-pending application are further evidence that the present patent application is fully enabling, because the target and the drug were discovered in less than three years through the work of far fewer employees, and using far fewer resources and expenses, as compared to drug discovery at a traditional pharmaceutical company.

I further declare that all statements made herein of my own knowledge are true and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code.

Shawn Iadonato, Ph.D.

State of Washington)
) ss.
County of *King*)

On this 18th day of December, 2006, before me, a Notary Public in and for the State and County aforesaid, personally appeared Shawn Iadonato, Ph.D. to me known and known to me to be the person of that name, who signed and sealed the foregoing instrument, and he acknowledged the same to be his free act and deed.

Notary Public

Commission expires 6-15-08

Shawn P. Iadonato, Ph.D.

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Profile

Accomplished life sciences entrepreneur with 10 years experience managing large biotech R&D programs. Founded and managed successful companies. Identified and validated drug targets. Directed successful preclinical drug development programs. Excellent patient recruiter and clinical study coordinator. Able strategic thinker and team builder.

Areas of Expertise

- Drug Discovery and Development
- Biotech R&D Operations
- Startup Companies
- Human Genetics and Genomics
- Virology, Protein Chemistry, and Primatology
- Preclinical ADME/TOX

Experience

ILLUMIGEN BIOSCIENCES INC. 2000-Present

Founder, Director, and Chief Scientific Officer

Founded and co-managed startup of drug discovery company. Led company's experimental R&D efforts resulting in the discovery and development of IB657, a novel anti-hepatitis C drug.

- Developed and implemented genomics-based drug discovery programs.
- Led effort to identify and validate drug targets and characterize lead compounds.
- Designed and implemented strategic drug development plans.
- Recruited top-level scientists into multidisciplinary teams.
- Established 13 clinical recruitment sites in three countries.
- Directed outsourced R&D activities.
- Generated R&D revenue >$1M per year.
- Assisted with corporate financings.
- Executed corporate and academic licensing agreements.
- Prepared patent applications and co-developed IP strategy.
- Prepared financial models and business plans.

LUCIDAS INFORMATION INC. 1998-1999

Founder and Vice President, Sequencing Technologies

Co-founded startup biotechnology firm. Led company's genomics and genetics R&D effort.

- Developed company's R&D and drug discovery strategies and programs.
- Drafted business plan documents and supported corporate financings.
- Prepared financial models.
- Prepared patent applications and co-developed company IP strategy.
- Assisted with legal and financial activities of the company.

UNIVERSITY OF WASHINGTON GENOME CENTER 1996-1998

Operational Manager and Research Scientist

Established the NIH-funded University of Washington Genome Center.

Established operations of the University of Washington Genome Center. Built, trained, and led a twenty-person R&D and data production team. Participated in sequencing the human, mouse, and microbial genomes. Prepared financial models and grant applications. Established the Center as the highest-quality data producer of the Human Genome Project.

Accomplishments

- Recipient of ~$1.6M in federal grant money (National Institutes of Health & Department of Defense) during previous three years.
- Inventor on multiple pending patent applications in the U.S. and abroad.
- *Ad Hoc* reviewer for the National Human Genome Research Institute (NIH), National Institute of Environmental Health Sciences (NIH), and U.S. Department of Agriculture.
- *Ad Hoc* reviewer for the publication *Genome Research.*
- Member, American Society of Human Genetics.

Selected Publications

- **Iadonato, S.P.**, Bu, G., Maksymovitch, E.A., and A.L. Schwartz (1993). Interaction of a 39 kDa protein with the low-density-lipoprotein-receptor-related-protein (LRP) on rat hepatoma cells. *Biochemical Journal **296:*** 867-875
- Gnirke, A., **Iadonato, S.P.**, Kwok, P.-Y, and M.V. Olson (1994). Physical calibration of yeast artifical chromosome contig maps by RecA-assisted restriction endonuclease (RARE) cleavage. *Genomics **24:*** 199-210.
- **Iadonato, S.P.** and A. Gnirke (1995). RARE-Cleavage Analysis of YACs. *Methods in Molecular Biology **54:*** 75-85.
- Trask, B.J., Friedman, C., Martin-Gallardo, A., Rowen, L., Akinbami, C., Blankenship, J., Collins, C., Giorgi, D., **Iadonato, S.P.**, Johnson, F., *et al.* (1998). Members of the olfactory receptor gene family are contained in large block of DNA duplicated polymorphically near the ends of human chromosomes. *Human Molecular Genetics **7:*** 13-26.
- International Human Genome Sequencing Consortium (2001). Initial sequencing and analysis of the human genome. *Nature **409:*** 860-921
- Hillier, L.W., Fulton, R.S., Fulton, L.A., Graves, T.A., Pepin, K.H., Wagner-McPherson, C., Layman, D., Maas, J., Jaeger, S., Walker, R., *et al.* (2003). The DNA sequence of human chromosome 7. *Nature **424:*** 157-164.
- Magness, C.L., Fellin, C.P, Thomas, M.J., Korth, M.J., Agy, M.B., Proll, S.C., Fitzgibbon, M., Scherer, C.A., Miner, D.G., Katze, M.G. and **S.P. Iadonato** (2005). Analysis of the *Macaca mulatta* transcriptome and the sequence divergence between *Macaca* and human. *Genome Biology* (In press).

Education

Ph.D., Genetics, University of Washington, Seattle, WA	1998
B.A., Biology, University of Pennsylvania, Philadelphia, PA	1991